SUPPLEMENTARY APPENDIX

Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and Phe508del and a Residual Function Mutation

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SUPPLEMENTAL METHODS

Criteria for Eligible Residual Function Mutations

Population-level clinical criteria for residual function mutations were an average sweat chloride level <86 mmol/L and incidence of pancreatic insufficiency ≤50%. Laboratory criteria for residual function were the presence of mature CFTR by Western blot and observed chloride transport in the absence of treatment in isogenic cell lines expressing the *CFTR* gene in question.[1] In vitro response to ivacaftor was defined by a statistically significant increase in chloride transport in the presence of ivacaftor compared to baseline and/or an increase in chloride transport of ≥ 10% over baseline. A list of eligible mutations leading to residual function are given in Table S1.

Prespecified Patient-Level Eligibility Criteria

If the sweat chloride value was <60 mmol/L, evidence of chronic sinopulmonary disease was required, including at least 1 of the following: persistent colonization/infection with typical cystic fibrosis pathogens, including *Staphylococcus aureus*, *Haemophilus influenzae*, and mucoid and nonmucoid *Pseudomonas aeruginosa*; chronic cough and sputum production; persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation); nasal polyps, chronic sinusitis; and radiographic or computed tomographic abnormalities of the paranasal sinuses.

Sample Size and Power

The null hypothesis tested was that the mean absolute change from study baseline in percentage of predicted forced expiratory volume in 1 second (FEV_1) to the average of the week 4 and week 8 measurements was the same for (i) tezacaftor-ivacaftor and placebo and (ii) ivacaftor monotherapy and placebo. The sample size of 34 patients per sequence was adequate to yield at least 90% power to detect a treatment difference of 3 percentage points between tezacaftor-ivacaftor and placebo comparing the mean values of the primary endpoint; assuming a drop-out rate of 10%. A standard deviation (SD) of 7 percentage points and 2-sided significance level of 0.05 was used in the sample size calculations. Accounting for the testing strategy, the proposed sample size yielded approximately an 85% chance of observing a statistically significant difference between ivacaftor monotherapy and placebo for the primary endpoint, under the assumption that ivacaftor monotherapy was also 3 percentage points better than placebo.

Analysis of Primary Endpoint Variables

The primary analysis model included the absolute change from study baseline in percentage of predicted FEV_1 to the average of the week 4 and week 8 measurements as the dependent variable and the following fixed effects: treatment, period, percentage of predicted FEV_1 at study baseline, and patient as a random effect. The within-patient covariance was assumed to have the same compound symmetry (CS) structure for sequences containing placebo treatment but was different from the CS structure for sequences containing active treatment in both periods. Denominator degrees of freedom for the F-test for fixed effects was estimated using the Kenward-Roger

approximation.[2] The estimated mean of the dependent variable, a 95% confidence interval (CI), and a 2-sided P value were provided for each treatment. Similarly, the estimated between-group treatment differences along with the corresponding 95% CI and 2-sided P values were presented. No imputation of missing data were performed. Patients who had data only for one of the periods had a data structure similar to a parallel-group trial. Assuming that these patients had dropped out at random, the mixed effects model combined the estimate of treatment effect based on such patients with the estimate from patients who had data in both treatment periods. The weights used for combining these two estimates is based on their precisions.

Mixed-Model for Repeated Measures Analysis of Primary Endpoint

An alternative approach to analyze the absolute change from study baseline in percentage of predicted FEV_1 was to use the mixed-model for repeated measures (MMRM) approach. In the MMRM analysis, the absolute change from study baseline at each postbaseline visit (day 15, week 4, and week 8) during each treatment period was the dependent variable. The fixed effects in the model were: treatment, period, visit within period, treatment-by-visit interaction, and percentage of predicted FEV_1 at study baseline. The within-patient covariance was assumed to be unstructured (UN) for levels of period and UN for visits within period. The direct product of the 2 produced the estimated covariance matrix (type = UN@UN in SAS Procedure Mixed). The denominator degrees of freedom for the F-test for fixed effects was estimated using the Kenward-Roger approximation.[2] The average change from study baseline in percentage of predicted FEV_1 at weeks 4 and 8 for each treatment was estimated using contrasts from the MMRM. The estimated difference between treatments was also estimated

similarly. The resultant estimates, the 95% CI, and 2-sided P value were presented. A similar approach was followed to present the estimates for each visit. Additionally, the estimated change at each visit and the 95% CI were plotted.

Subgroup Analysis of the Primary Efficacy Endpoint

The subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis. The primary result obtained from the model was the estimated difference between the treatment groups. The following subgroups were considered:

- Age at screening (<18 and ≥18 years)
- Percentage of predicted FEV_1 at study baseline (<40, ≥40 to <70, and ≥70)
- Residual function mutation type (CFTR class V noncanonical splice vs. CFTR classes II to IV residual function)
- Sex
- Region (North America and Europe [including Israel and Australia])
- Use of inhaled antibiotic (Yes, No)
- Use of inhaled bronchodilator (Yes, No)
- Use of inhaled hypertonic saline (Yes, No)
- Use of inhaled corticosteroids (Yes, No)
- Use of azithromycin (Yes, No)
- Colonization of *Pseudomonas aeruginosa* (Positive, Negative)

Each of the above subgrouping factors utilized a model analogous to the one used for the primary analysis but included an additional covariate for the relevant grouping factor

as well as a term for interaction with treatment. For the subgroup analysis on percentage of predicted FEV_1 severity at study baseline, the term percentage of predicted FEV_1 at study baseline was removed from the primary analysis model to avoid redundancy. For each subgroup, the estimated mean of the primary endpoint, the corresponding 95% CI and 2-sided P value are presented by treatment group. Similarly, the estimated between-group treatment differences along with the corresponding 95% CI and 2-sided P values are presented. The estimated between-group treatment differences in different subgroup categories were presented in a forest plot.

Analysis of Key Secondary Efficacy Endpoint

Analysis for the absolute change from study baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (pooled 'Children Ages 12 and 13' version and 'Adolescents and Adults' version) score to the average of week 4 and week 8 scores in each treatment period was similar to the primary analysis of the primary efficacy endpoint. However, percentage of predicted FEV_1 at study baseline was replaced by CFQ-R respiratory domain score at study baseline in the model.

Other Secondary Endpoints

Other secondary endpoints include (i) relative change in percentage of predicted FEV_1 and (ii) absolute change in sweat chloride from study baseline to the average of the week 4 and week 8 measurements in each treatment period. The analysis was similar to the primary analysis of the primary efficacy endpoint. However, for the analysis of

absolute change in sweat chloride the percentage of predicted FEV_1 study baseline was replaced by sweat chloride at study baseline in the model.

Multiplicity Adjustment

The testing strategy considered the comparison of tezacaftor-ivacaftor versus placebo and ivacaftor monotherapy versus placebo. To control for multiplicity of endpoints and treatments (the probability of Type 1 error), each endpoint was to be assessed sequentially using a gatekeeping approach where statistical significance could be claimed for the key secondary endpoint only if the primary endpoint met the requirements for significance. Additionally, as there were two treatment comparisons for each endpoint, the gatekeeping approach was applied (i.e., ivacaftor monotherapy for a given endpoint could achieve significance only if the comparison for tezacaftor-ivacaftor for the same endpoint was significant). For each endpoint, and for each treatment group, the comparison with placebo was to be conducted using a significance level (alpha) set at 0.05 (2-sided).

SUPPLEMENTAL RESULTS

Exploratory and Additional Supportive Endpoints

The mean absolute change from study baseline in body mass index (BMI) at week 8 was 0.34 kg/m^2 for tezacaftor-ivacaftor, 0.47 kg/m^2 for ivacaftor, and 0.18 kg/m^2 for placebo. The short treatment duration may have affected sensitivity to detect changes in BMI.

Although the study was not powered to evaluate changes in the rate of pulmonary exacerbation, the estimated event rate of pulmonary exacerbation was lower for tezacaftor-ivacaftor (0.34 events per year) and ivacaftor (0.29 events per year) than for placebo (0.63 events per year), noting these changes did not reach statistical significance. Compared with placebo, the rate ratio was 0.54 (95% CI: 0.26, 1.13) for tezacaftor-ivacaftor and 0.46 (95% CI: 0.21, 1.01) for ivacaftor (Table 2). The rate ratio was 1.18 (95% CI: 0.49, 2.87) for tezacaftor-ivacaftor compared with ivacaftor (Table 2).

Treatment with tezacaftor-ivacaftor and ivacaftor resulted in reduction of mean immunoreactive trypsinogen levels by day 15 that were sustained through week 8. The within-group mean change in immunoreactive trypsinogen from study baseline to week 8 was −18.1 ng/mL in the tezacaftor-ivacaftor group, −23.2 ng/mL in the ivacaftor group, and −2.1 ng/mL in the placebo group (Table 2).

At study baseline, the mean fecal elastase-1 value was 412.4 µg/g in the tezacaftor-ivacaftor group, 405.8 µg/g in the ivacaftor group, and 414.4 µg/g in the placebo group; a total of 22 (13.7%) patients in the tezacaftor-ivacaftor group, 22 (14.1%) patients in the ivacaftor group, and 21 (13.0%) patients in the placebo group had <200 µg/g of fecal elastase-1 (pancreatic insufficiency) at study baseline, reflecting a high prevalence of pancreatic sufficiency at baseline. The within-group mean change in fecal elastase-1 from study baseline to the average of week 4 and week 8 was −3.4 µg/g in the tezacaftor-ivacaftor group, −16.1 µg/g in the ivacaftor group, and −23.1 µg/g in the placebo group (Table 2). Among patients with values <200 µg/g at study baseline, 6 (27.2%) patients in the tezacaftor-ivacaftor group, 4 (18.2%) patients in the ivacaftor

group, and 1 (4.8%) patient in the placebo group had maximum fecal elastase-1 values ≥200 µg/g at week 4 and week 8.

Safety

Additional Information on Adverse Events

Serious and life-threatening adverse events are reported in the main text. Serious adverse events, a subset of the above, occurred in 8 (4.9%) patients in the tezacaftor-ivacaftor group, 10 (6.4%) patients in the ivacaftor group, and 14 (8.6%) patients in the placebo group (Table 3).

Adverse events that led to treatment discontinuation are reported in the main text. Adverse events led to treatment interruption in 2 (1.2%) patients in the tezacaftor-ivacaftor group, 5 (3.2%) patients in the ivacaftor group, and 6 (3.7%) patients in the placebo group.

Respiratory Adverse Events

Increased monitoring was conducted for respiratory adverse events because of the increased prevalence of acute but transient respiratory adverse events associated with the CFTR corrector lumacaftor.[3-5] Adverse events associated with respiratory events occurred in 14 (8.6%) patients in the tezacaftor-ivacaftor group, 7 (4.5%) patients in the ivacaftor group, and 22 (13.6%) patients in the placebo group (Table S2 in the Supplementary Appendix). Overall and by preferred term, most adverse events associated with respiratory events either occurred at a similar incidence between the 3 treatment groups or were more common in the placebo group than in the ivacaftor or tezacaftor-ivacaftor groups. Respiratory events were mild to moderate in severity across

all treatment groups, and there were no grade 3 or 4 respiratory events. There were no respiratory events that were serious or led to death.

Adverse events associated with respiratory symptoms (chest discomfort, dyspnea, and respiration abnormal), occurred in 11 (6.8%) patients in the tezacaftor-ivacaftor group, 3 (1.9%) patients in the ivacaftor group, and 16 (9.9%) patients in the placebo group. The events either occurred at a similar incidence between the 3 treatment groups or were more common in the placebo group than in the ivacaftor or tezacaftor-ivacaftor groups. The time-to-onset of the first adverse event associated with respiratory events and symptoms was similar in all 3 treatment groups.

Acute Effects on Spirometry

Postdose spirometry assessments were performed for patients (n=21, 20, and 24 for tezacaftor-ivacaftor, ivacaftor and placebo, respectively) between the ages of 12 and 18 years. The postdose (2- and 4-hour) percentage of predicted FEV_1 values showed no evidence of acute decline from the predose values on both days 1 and 15 for either tezacaftor-ivacaftor or ivacaftor (Table S3 in the Supplementary Appendix).

Liver Function Tests

Few patients had elevations in liver transaminases or total bilirubin during the study period (Table S4), and no patients experienced an elevated transaminase > 3 x ULN concurrent with an elevated total bilirubin > 2 x ULN. One (0.6%) patient in the placebo group, 3 (1.9%) patients in the ivacaftor group, and 1 (0.6%) patient in the tezacaftor-ivacaftor group had transaminase elevations >3 × upper limit of normal (ULN). Two

(1.3%) patients in the ivacaftor group had transaminase elevations >5 × ULN. No patient had transaminase elevations >8 × ULN during the treatment period. One (0.6%) patient in the placebo group, 2 (1.3%) patients in the ivacaftor group, and 2 (1.2%) patients in the tezacaftor-ivacaftor group had total bilirubin elevations >2 × ULN. None of these were serious or led to treatment discontinuation, and the majority were assessed as mild or moderate by the investigator.

SUPPLEMENTAL DISCUSSION

Residual pancreatic function allows for the potential to preserve organ function or delay the onset of pancreatic insufficiency with early CFTR modulation treatment. Fecal elastase-1 did not significantly change and the majority of subjects met the criteria for pancreatic sufficiency at baseline (FE-1 >200 μg/g); in contrast, serum immunoreactive trypsinogen suggested active treatment may improve pancreatic injury in patients with residual pancreatic secretion. Similar immunoreactive trypsinogen responses were seen with ivacaftor in 2- to 5-year old patients with cystic fibrosis carrying the *G551D* allele.[6] Further study of the potential for pancreatic organ preservation is warranted, targeting patients early in life, before organ damage is less reversible. Similarly, the potential to reduce pulmonary exacerbations and increase BMI over long-term treatment requires further study and may raise unique issues in patients with residual function since exacerbations can be less frequent in this population.

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SUPPLEMENTAL TABLES

Table S1. Eligible Residual Function Mutations

Noncanonical splice mutations	no.
2789+5G→A	37
3849+10kbC→T	69
3272-26A→G	36
711+3A→G	3
Missense mutations	
E56K	0
P67L	17
E831X	1
R74W	0
D110E	0
D110H	1
R117C	1
E193K	0
L206W	5
R347H	4
R352Q	3
R1070W	3
A455E	20
F1074L	0
D579G	3
D1152H	26
S945L	13
D1270N	0
S977F	2
F1052V	0
K1060T	0

Table S2. Summary of Treatment-Emergent Respiratory Events by Preferred Term, Safety Set.

	Placebo N=162 no. (%)	Ivacaftor N=157 no. (%)	Tezacaftor-Ivacaftor N=162 no. (%)
Any AEs (respiratory events)	22 (13.6)	7 (4.5)	14 (8.6)
Chest discomfort	0	0	2 (1.2)
Dyspnea	11 (6.8)	3 (1.9)	9 (5.6)
Respiration abnormal	5 (3.1)	0	3 (1.9)
Asthma	3 (1.9)	0	0
Bronchial hyperreactivity	0	0	0
Bronchospasm	2 (1.2)	0	0
Wheezing	3 (1.9)	4 (2.5)	3 (1.9)
Any respiratory events by maximum severity	22 (13.6)	7 (4.5)	14 (8.6)
Mild	12 (7.4)	5 (3.2)	12 (7.4)
Moderate	10 (6.2)	2 (1.3)	2 (1.2)
Severe	0	0	0
Life-threatening	0	0	0
Missing	0	0	0
Events leading to treatment discontinuation	1 (0.6)	0	0
Serious events	0	0	0
Related serious events	0	0	0
Events leading to death	0	0	0
By time interval			
Patients with any respiratory events			
>0 to ≤1 week	5 (3.1)	1 (0.6)	4 (2.5)
>1 to ≤2 weeks	1 (0.6)	1 (0.6)	1 (0.6)
>0 to ≤8 weeks	15 (9.3)	5 (3.2)	9 (5.6)
>8 weeks	7 (4.3)	2 (1.3)	7 (4.3)

AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities.
Note: Respiratory events were coded using MedDRA Version 19.1. If a patient had multiple events within a category, system organ class, or preferred term, the patient was counted only once. Related serious events include related, possibly related, and missing categories.

Table S3. Mean (SD) Change from Predose to Post Dose in Percentage of Predicted FEV_1 on Days 1 and 15, Safety Set for Patients ⩾12 to <18 Years Old at Screening.

	Placebo N=24	Ivacaftor N=20	Tezacaftor-Ivacaftor N=21
Day 1			
no.	12	12	13
2 hours post dose	-0.5 (3.9)	0.9 (5.7)	0.5 (3.6)
no.	12	13	14
4 hours post dose	-0.3 (4.8)	-0.4 (6.8)	0.9 (3.9)
Day 15			
no.	13	12	12
2 hours post dose	1.3 (3.6)	1.9 (2.4)	1.4 (2.5)
no.	13	12	10
4 hours post dose	0.7 (4.1)	2.9 (5.1)	1.8 (3.4)

FEV_1, forced expiratory volume in 1 second; no., size of subsample; N, total sample size; SD, standard deviation.

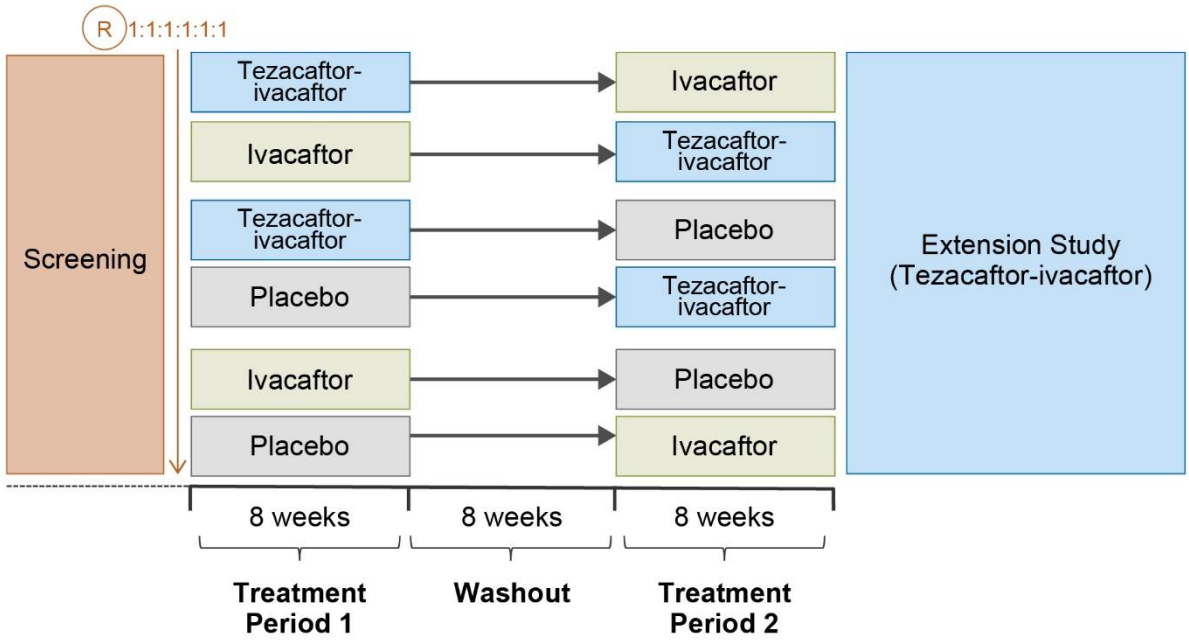
Table S4. Liver Transaminase and Bilirubin Elevations During the Study Period.

Parameter	Placebo N=162	Ivacaftor N=157	Tezacaftor-Ivacaftor N=162
Alanine aminotransferase — n/N1 (%)			
>ULN to ≤3x ULN	12/162 (7.4)	18/157 (11.5)	18/162 (11.1)
>3x to ≤5x ULN	1/162 (0.6)	3/157 (1.9)	1/162 (0.6)
>5x ULN	0/162	0/157	0/162
Aspartate aminotransferase — n/N1 (%)			
>ULN to ≤3x ULN	17/162 (10.5)	21/157 (13.4)	23/162 (14.2)
>3x to ≤5x ULN	0/162	2/157 (1.3)	1/162 (0.6)
>5x ULN	0/162	2/157 (1.3)	0/162
Total bilirubin — n/N1 (%)			
>1.5x ULN to ≤2x ULN	0/162	3/157 (1.9)	2/162 (1.2)
>2x ULN to ≤3x ULN	1/162 (0.6)	2/157 (1.3)	2/162 (1.2)
>3x ULN	0/162	0/157	0/162

ULN, upper limit of normal.

SUPPLEMENTAL FIGURES

Figure S1. Study Design.



R, randomized.

Figure S2. CONSORT Diagram.